REMARKS

Applicants thank the Examiner for the very thorough consideration given the present application. Claims 1-8 are now present in this application. No new matter has been added by way of the present amendment. For instance, amended claims 1, 2 and 6 are supported by the present specification at, for example, page 6, lines 1-4. Claims 4 and 7 have been amended to correct typographical errors. Accordingly, no new matter has been added.

In view of the following amendments and remarks, Applicants respectfully request that the Examiner withdraw all outstanding rejections and allow the currently pending claims.

Objections to the title

The Examiner has objected to the title of the invention, stating that it is non-descriptive. The Examiner has required a new title that is clearly indicative of the invention to which the claims are directed.

Applicants have amended the title in accordance with the Examiner's suggestions.

It is respectfully submitted that the new title is descriptive and clearly indicative of the invention claimed. Accordingly, reconsideration and withdrawal of this objection are respectfully requested.

Claim Objections

The Examiner has objected to claims 4 and 7 because of minor informalities.

Applicants have thoroughly reviewed and amended the claims to correct such informalities.

Reconsideration and withdrawal of this objection are respectfully requested.

Obviousness-Type Double Patenting Issues

Claims 1-8 stand provisionally rejected under the judicially created doctrine of double patenting over claims 7-11 and 17-19 of U.S. Patent No. 6,677,124. This rejection is respectfully traversed.

The Examiner states that "there is no apparent reason why Applicant was prevented from presenting claims corresponding to those of the instant application during prosecution of the application which matured into a patent." Furthermore, the Examiner notes that a timely filed Terminal Disclaimer in compliance with 37 C.F.R. § 1.321(b) may be used to overcome the provisional rejection.

It is noted, however, that the instant application is a Divisional of co-pending application No. 09/942,709, filed on August 31, 2001 and now U.S. Patent No. 6,677,124. Accordingly, Applicant was prevented from presenting the claims corresponding to those of the instant application during prosecution of application No. 09/942,709. Furthermore, it is respectfully submitted that the Examiner cannot require a terminal disclaimer in this case unless the presently claimed subject matter diverges from that originally filed.

Accordingly, it is submitted that this rejection is moot. Reconsideration and withdrawal of this rejection are thus respectfully requested.

Issues Under 35 U.S.C. § 112, First Paragraph

Claims 1-3 and 6-8 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement requirement. Claims 1-3 and 6-8 also stand rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. These rejections are respectfully traversed.

The Examiner states that the specification does not provide enablement for "a first antibody that is polyclonal or monoclonal." The Examiner further states that the disclosure, as filed, does not support the use of the generic language in which the antibodies recognize two different regions of hBNP.

Applicants submit that the specification provides enablement for a first polyclonal or monoclonal antibody and supports the generic language with regard to recognition of different regions of hBNP at, for example, page 6, lines 1-7. Applicants have disclosed that hBNP has a ring structure and that antibody B, in one **preferred** embodiment (emphasis added), could be a monoclonal antibody. Because the first antibody recognizes hBNP at a site different from that recognized by the second antibody (page 6, lines 3-4), it follows that the first antibody could be a polyclonal antibody.

With regard to the antibodies recognizing different regions of nBNP, it is well established that:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts.

MPEP §2164.08, quoting *In re Goffe*, 542 F.2d 564, 567, 191 USPQ 429, 431 (CCPA 1976),

The Applicants respectfully submit that the claims are fully enabled as written. The steps of contacting a solution with two defined antibodies would be completely clear to one of skill in the art. The Applicants have fully demonstrated how to make and use the full scope of their invention. The specification does not limit the region of hBNP that the second antibody recognizes. It is improper for the Office to impose such a limitation without a proper basis. The Applicants respectfully submit that the highly sensitive assay of the present invention will work as presently claimed. The Office Action provides no reason or explanation why the invention will not work as presently claimed.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, are respectfully requested.

Issues Under 35 U.S.C. § 112, Second Paragraph

Claims 2, 3-5 and 7 stand rejected under 35 U.S.C. § 112, second paragraph for reciting limitations that lack sufficient antecedent basis. These rejections are respectfully traversed.

In regard to claim 2, it is noted that the limitation "said Fab' fragment" has sufficient antecedent basis in claim 1 at, for example, 1(a). Accordingly, this rejection is moot.

In regard to claims 3-5 and 7, Applicant submits that these claims have been amended to more clearly recite the subject matter which Applicant regards as his invention. As amended, claim 1 is directed to a "first antibody" and a "second antibody", thereby providing sufficient antecedent

basis for the limitation "said first (or second) antibody" of claims 3-5 and 7. Accordingly, this rejection is moot.

Reconsideration and withdrawal of these rejections are hereby respectfully requested.

Issues Under 35 U.S.C. § 103

Claims 1, 2, 6 and 8 stand rejected under 35 U.S.C. § 103 as being unpatentable over Itoh et al. (Endocrinology, 1990 Sep; 127(3): 1292-1300)(hereinafter Itoh et al.) in view of Takeyama et al. (1990 Jul 3; 130 (2): 217-22)(hereinafter Takeyama et al.), in view of Sutcliffe et al. (1983 Feb 11; 219(4585): 660-6)(hereinafter Sutcliffe et al.), in view of Harlow et al. (Antibodies, A Laboratory Manual. 1988. Cold Spring Harbor Laboratory. pp 578-582)(hereinafter Harlow et al.), in view of Hashida et al. (Clinica Chimica Acta 1988 175:11-1)(hereinafter Hashida et al.) and in view of Bulinski (Intl Rev Cytology 1986; 103: 281-302)(hereinafter Bulinski). This rejection is respectfully traversed.

At the outset, it is noted that claims 3-5 and 7 have not been rejected under 35 U.S.C. § 103 based upon prior art. Applicant assumes that the subject matter set forth in claims 3-5 and 7 is therefore considered patentable over the prior art. Accordingly, it is submitted that claims 3-4 and 7 are in condition for allowance.

In regard to claims 1, 2, 6 and 8, none of the cited prior art shows or suggests a combination as claimed, which includes the use of a solution containing hBNP with an enzyme-conjugated or radioisotope-labeled Fab' fragment of a first antibody which is reactive with a first, N-terminal region of hBNP and a second antibody reactive with a second, C-terminal region of hBNP having an amino acid sequence lys-val-leu-arg-arg-his to produce complexes

which are subsequently contacted with an immobilized antibody reactive with the Fc fragment of said second antibody to produce further complexes, which are then contacted with a substrate of an enzyme-conjugated antibody in an appropriate reaction buffer and incubated so as to allow formation of an enzymatic reaction end product, wherein the amount of said end product or the amount of radioactivity bound to the further complexes is determined and related to the amount of hBNP.

As acknowledged by the Examiner, Itoh et al. merely discloses the production of monoclonal antibodies to brain natriuretic peptide. None of the cited references, alone or in combination, overcome the deficiencies of Itoh et al. For example, although Hashida et al. discloses C-terminal specificity, the assay disclosed by Hashida et al. does not anticipate the immunoassay of the present invention. Hashida et al. discloses an immunoassay wherein a sample is first added to an immobilized antibody before any further steps have taken place (see, for example, page 13). In stark contrast, the instant invention is directed to a sample that is contacted with an immobilized antibody after it has been contacted with **two different kinds of antibodies** (emphasis added).

The other references cited by the Examiner equally fail to render the instant invention obvious. Sutcliffe et al., for example, teaches peptide immunogens with predetermined specificity without any teachings of C-terminal specificity. Takeyama et al. teaches the sequences of porcine and human BNP. Harlow et al. teaches sandwich immunoassays. Bulinski discloses certain well known methods for preparation of peptide antibodies, none of which render the present invention obvious.

It is respectfully submitted that the 35 U.S.C. 103 rejection of Itoh et al. in view of Takeyama et al., in view of Sutcliffe et al., in view of Harlow et al., in view of Hashida et al. and in view of Bulinski must be withdrawn. Each and every element of independent claims 1, 6 and 8 is not shown, taught or disclosed by the combination. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 165 USPQ 494, 496 (CCPA 1970); MPEP 2143.03.

Furthermore, Applicants respectfully submit that there is no motivation to combine the references cited by the Examiner. References cannot be arbitrarily combined. There must be some reason why one of ordinary skill in the art would be motivated to make the proposed combination of the primary and secondary references. In re Nomiya, 184 USPQ 607 (CCPA 1975). The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin 170 USPQ 209 (CCPA 1971). The Examiner is requested to cite a motivation, other than hindsight gleaned from Applicants' invention, to combine all of the cited references.

Because the combinations, as set forth in Applicants' claims, are not disclosed or made obvious by the cited prior art, reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact J. Mark Konieczny (Reg. No. 47,715) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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